IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ABBOTT GMBH & CO., KG, ABBOTT BIORESEARCH CENTER, INC. AND ABBOTT BIOTECHNOLOGY LTD.,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 4:09-cv-11340-FDS
CENTOCOR ORTHO BIOTECH, INC. AND CENTOCOR BIOLOGICS, LLC.,	)	
Defendants.	)	

PLAINTIFFS' REPLY CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

As set forth in Abbott's Opening Brief, each of its proposed claim constructions comply with Federal Circuit precedent requiring claim terms "generally [be] given their ordinary and customary meaning" as understood by one of ordinary skill in the art. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). In contrast, Centocor's proposed constructions deviate from the ordinary and customary meaning of the terms in an effort to limit the scope of the claims to examples and embodiments set forth in the specification. Centocor's approach of seeking to import limitations from the specification into the claims – and thus each of Centocor's proposed constructions – violate clear Federal Circuit precedent. *See e.g.*, *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1117 (Fed. Cir. 2004) (holding "particular embodiments appearing in the written description will not be used to limit claim language that has broader effect"); *Phillips*, 415 F.3d at 1313. Accordingly, the Court should reject Centocor's proposed constructions, and, instead, adopt Abbott's proposed constructions of the disputed terms.

II. ARGUMENT

A. The Claims

The disputed claim terms are exemplified by claims 7, 8, 13 (each of which depends from claim 1), and 61 (which depends from claims 50 and 52) of the '128 Patent and claim 1 of the '485 Patent. These claims are set forth below, with the relevant disputed terms highlighted in bold, for reference:

'128 patent claims

1. An isolated human antibody, or antigen-binding portion thereof that binds to human IL-12 and dissociates from human IL-12 with a K_d of 1 x

10^{-10} M or less and a k_{off} rate constant of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance.

7. The isolated human antibody of any one of claims 1 to 3, wherein the antibody is a **neutralizing antibody**.

8. The neutralizing antibody of claim 7, or an antigen-binding portion thereof, which **inhibits phytohemagglutinin blast proliferation in an in vitro PHA assay** with an IC_{50} of 1 x 10^{-9} M or less.

13. The neutralizing antibody of claim 7, or an antigen-binding portion thereof, which **inhibits human IFNγ production** with an IC_{50} of 1 x 10^{-10} M or less.

50. An isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a K_d of 1.34 x 10^{-10} M or less, and neutralizes human IL-12.

52. The isolated human antibody, or antigen-binding portion thereof, of claim 50 or 51, which is a recombinant antibody, or antigen-binding portion thereof.

61. The isolated human antibody of claim 52, or an antigen-binding portion thereof, which **inhibits IL-12 binding to its receptor in an IL-12 receptor binding assay (RBA)** with an IC_{50} of 1 x 10^{-9} M or less.

'485 patent claim

1. A pharmaceutical composition comprising an isolated human antibody, or antigen-binding portion thereof, which is capable of binding to an epitope of the p40 subunit of IL-12, and further comprising an **additional agent**.

B. "neutralizing antibody"

Abbott's proposed construction of "neutralizing antibody" should be adopted, as it is supported by the language of the claims and specification. *See Phillips*, 415 F.3d at 1314.

CLAIM TERM	ABBOTT'S PROPOSED CONSTRUCTION	CENTOCOR'S PROPOSED CONSTRUCTION
"neutralizing antibody"	"an antibody whose binding to an antigen results in inhibition of a biological activity"	"results in inhibition of the biological activity of human IL-12"

Defendants make two legally unsupportable arguments in their effort to urge the Court to narrow the asserted claims. ***First***, relying upon selective quotations to the specification, Defendants' argue that the claim requires inhibition of "***the*** biological activity" as opposed to "***a*** biological activity." (*See* Def. Br. at 9.) In particular, the Defendants argue that "the asserted patents define the term 'neutralizing antibody' as 'an antibody whose binding to hIL-12 results in inhibition of ***the*** biological activity of hIL-12.'" (*See id.*) But, as set forth in Abbott's Opening Brief, a review of the entire passage that Defendants cite – as opposed to the portion they quote – makes clear that the language quoted by Defendants is not a definition, but an example:

> A "neutralizing antibody" (or an antibody that neutralized hIL-12 activity") ***includes*** an antibody whose binding to hIL-12 results in inhibition of the biological activity of hIL-12. The inhibition of the biological activity of hIL-12 can be assessed by measuring one or more indicators of hIL-12 biological activity….

(col. 27, ll. 53-65 (emphasis added).) According to this language, while an antibody whose binding to human IL-12 results in the inhibition of the biological activity of human IL-12 would be included as a "neutralizing antibody," this term is not limited to an antibody with that specific characteristic. Indeed, Centocor's own tutorial to the PTO (submitted as part of the Interference concerning certain claims of the '128 patent) correctly defined "neutralization" as occurring when the antibody neutralizes ***a*** biological activity:

> [n]eutralization refers to the ability of an antibody to inhibit ***one or more biological activities*** of the antigen to which it binds. Accordingly, the ability of an antibody to "neutralize" an antigen may be evaluated by examining the extent to which presence of the antibody in an experimental system affects ***a biological activity*** of the antigen.

(*See* Def. Br., Ex. 2 at 7 (emphasis added).)

Second, Defendants incorrectly argue that Abbott's proposed construction "reads out IL-12 from the claims." (*See* Def. Br. at 9-10.) This is untrue. To be sure, Abbott's claim construction does not read IL-12 into the claim phrase "neutralizing antibody;" in fact, other

words in the asserted claims of the '128 patent explicitly require a human antibody that "binds to IL-12." (*See e.g.*, '128 patent, claim 1.) As discussed in Abbott's Opening Brief, however, there are also claims from the '485 patent that recite binding to the p40 subunit (*see* claims 15 and 25 of the '485 patent). (*See* Abbott's Opening Br. at 14-16.) By relying solely upon the selective quotation above, Defendants improperly attempt to narrow the claims to only IL-12, excluding antibodies that neutralize activity of an antigen (p40) expressly included in the claims and specification.

C. Disputed Assay-Related Claim Terms

As set forth in the parties' Opening Briefs and below, there are three disputed claim limitations related to known "assays" or tests for measuring the inhibitory effect of an antibody to a cytokine.

CLAIM TERM	ABBOTT'S PROPOSED CONSTRUCTION	CENTOCOR'S PROPOSED CONSTRUCTION
"inhibits phytohemagglutinin blast proliferation in an in vitro PHA assay" or "inhibits phytohemagglutinin blast proliferation in an in vitro phytohemagglutinin blast proliferation assay (PHA) assay"	"inhibits the proliferation of stimulated human PHA blasts"	"inhibits the proliferation of human PHA blasts stimulated by IL-12"
"inhibits human IFNγ production"	"inhibits human IFNγ production in either an *in vitro* or *in vivo* assay"	"inhibits the production of human interferon-γ by human PHA blasts stimulated by IL-12"
"inhibits IL-12 binding to its receptor in an IL-12 receptor binding assay (RBA)"	Plain meaning	"inhibits IL-12 binding to IL-12 receptors on human PHA blasts"

Abbott's proposed constructions for each of these assay-related limitations should be adopted, as they are consistent with the claim language, the specification, and the state of the art. *See Phillips*, 415 F.3d at 1314. Indeed, there is no real dispute about the meaning of the ***words***

of the claims; neither party proposes, for example, a definition of "proliferation" or "human IFNγ." Instead of seeking an interpretation of the claim terms, Defendants simply seeks to add additional limitations that are not in the claim. Defendants' proposed constructions therefore, represent an attempt to amend rather than interpret the words of the claims.

The only support Defendants provide for their proposed construction of each of these three assay related terms is a citation to Example 1 in the specification. (*See* Def. Br. at 10-14.) The Defendants have not and cannot point to any express surrender of claim scope as required by the Federal Circuit to narrow a claim term to an example set forth in the specification. *See Innova/Pure Water, Inc.*, 381 F.3d at 1117. Moreover, Defendants' attempt to limit the claims to the examples in the specification does not even accurately reflect those examples.

First, in support of their attempt to limit "inhibits phytohemagglutinin blast proliferation in an intro PHA assay" to "inhibits the proliferation of human PHA blasts stimulated by IL-12", Centocor incorrectly states that "Abbott's construction allows for the possibility that the PHA blast cells could be stimulated with something other than IL-12, which is not supported by the specification," and that "[t]here is no teaching in the asserted specifications of the stimulating PHA blast cells with anything other than IL-12." (*See* Def. Br. at 11.) This is simply not true. Example 3.A. describes the preparation of PHA blast cells for, *inter alia,* cell proliferation using IL-2 to incubate the cells. (*See* col. 109, l. 38 – col. 110, l. 6.)

Second, in an effort to limit "inhibits IFNγ production" to "inhibits the production of human interferon-γ by human PHA blasts stimulated by IL-12," Centocor erroneously argues that "[t]here is no description and no indication in the specifications that this assay could be performed *in vivo* . . . ." (*See* Def. Br. at 13.) But as discussed in Abbott's Opening Brief at

pages 17-19, Example 4 explicitly describes monitoring IFNγ *in vivo* in various animal models. (*See* col. 113, l. 58 – col. 116, l. 18.)

Finally, Centocor attempts to limit "inhibits IL-12 binding to its receptor in an IL-12 receptor binding assay (RBA)" to receptor binding assays performed with PHA blast cells, arguing that the specification provides no other examples. (*See* Def. Br. at 13-14.) But to properly construe clams, courts must examine not just the specification, but also the state of the art at the time. *See Phillips*, 415 F.3d at 1314. Here, as shown by contemporaneous scientific references, other "IL-12 receptor binding assay[s]" were known at the time the provisional application was filed. (*See* Gunther Decl., Ex. 8; Grusby Decl. at ¶¶ 23, 29.)

D. "additional agent"[1]

As with the other disputed terms, Defendants' proposed construction of "additional agent" should be rejected, as it improperly attempts to narrow the scope of the claim.

CLAIM TERM	ABBOTT'S PROPOSED CONSTRUCTION	CENTOCOR'S PROPOSED CONSTRUCTION
"additional agent"	Plain meaning	"an agent other than a pharmaceutically acceptable carrier which imparts a beneficial attribute to the therapeutic composition"

The parties agree that Centocor's proposed construction – which excludes pharmaceutically acceptable carrier[s] – flatly contradicts the patent specification. (*See* Def. Br. at 15.) Centocor explicitly concedes this fact: "[a]s set forth in the specification, the term ["additional agent"] would be broad enough to include therapeutic agents and 'pharmaceutically acceptable carriers.'" (*See id*.) Despite this concession, Centocor argues that Abbott

"surrendered 'pharmaceutically acceptable carriers' from the scope of the term 'additional agents' during prosecution of the 485 patent." (*See id*.) Centocor's argument is wrong as a matter of law and fact.

While the prosecution history of the patent can further inform the meaning of claim terms by demonstrating how the inventors understood the claimed invention, given its ambiguity, the prosecution history is less important than the other intrinsic evidence. *See Phillips*, 415 F.3d at 1317 ("[B]ecause the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes."). Thus, in order for statements made during prosecution to narrow the plain and ordinary meaning of the claim language as evidenced by the claim terms and the specification, the party seeking to impose such a narrower interpretation "must demonstrate an 'unambiguous' disclaimer, based on 'clear and unmistakable evidence' that some of the scope that would otherwise be captured by the claim was relinquished during prosecution." *Power Integrations, Inc. v. Fairchild Semiconductor Intern., Inc.*, Civ. No. 08-309-JJF-LPS, 2009 WL 4928029, at *15 (D. Del. Dec. 18, 2009) (quoting *Voda v. Cordis Corp.*, 536 F.3d 1311, 1321 (Fed. Cir. 2008)); *see also Middleton, Inc. v. Minn. Mining & Mfg. Co.,* 311 F.3d 1384, 1388 (Fed. Cir. 2002).

In determining whether prosecution disclaimer applies, a court should not read particular statements in isolation, but rather "assess whether a patentee relinquished a particular claim construction based on the totality of the prosecution history." *Rheox, Inc. v. Entact, Inc.*, 276 F.3d 1319, 1326 (Fed. Cir. 2002); *see also St. Clair Intellectual Prop. Consultants, Inc. v.*

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[1] "Additional agent" is only used in the '485 patent claims and not in the '128 patent claims. Therefore, the references in this section are to the '485 patent claims and specification.

Matshushita Elec. Indus. Co., C.A. No. 04-1436-JJF-LPS, 2009 WL 3834541, at *13 (D. Del. Nov. 13, 2009) (rejecting prosecution disclaimer argument that read the disputed statements out of context). A general disavowal will not suffice; "the statements or disavowals must directly address the disputed term." *Sky Technologies, LLC v. Ariba, Inc.*, 491 F. Supp. 2d 154, 158 (D. Mass. 2007). Likewise, there is no "clear and unmistakable" disclaimer if a prosecution argument is subject to more than one reasonable interpretation, one of which is consistent with a proffered meaning of the disputed term. *See Golight, Inc. v. Wal-Mart Stores, Inc.,* 355 F.3d 1327, 1332 (Fed. Cir. 2004) (finding no disclaimer because "the statements in the prosecution history are subject to multiple reasonable interpretations, they do not constitute a clear and unmistakable departure from the ordinary meaning of the term [at issue]"); *Cordis Corp. v. Medtronic AVE, Inc.,* 339 F.3d 1352, 1359 (Fed. Cir. 2003) (concluding that a statement made during prosecution "is amenable to multiple reasonable interpretations and it therefore does not constitute a clear and unmistakable surrender").

Moreover, "it is the applicant, not the examiner, who must give up or disclaim subject matter that would otherwise fall within the scope of the claims." *See Innova/Pure Water, Inc.,* 381 at 1124; see also *Bell Atl. Network Servs., Inc. v. Covad Commc'ns Group, Inc*., 262 F.3d 1258, 1273 (Fed. Cir. 2001) (unlike the statement of an applicant, the statements of an examiner will not necessarily limit a claim). Similarly, drawing inferences regarding the meaning of a claim term from a patent examiner's silence is not a proper basis on which to construe a patent claim. *See DeMarini Sports, Inc. v. Worth, Inc.,* 239 F.3d 1314, 1326 (Fed. Cir. 2001).

Here, there was no surrender of subject matter at all, much less a "clear and unmistakable one." During prosecution of the '485 patent, Abbott never discussed the meaning of "additional agent" or "pharmaceutically acceptable carrier" at all, and it certainly never clearly and

unambiguously disavowed a construction of "additional agent" that would include "pharmaceutically acceptable carriers." *See Voda*, 536 F.3d at 1321; *Golight, Inc.*, 355 F.3d at 1332; *Middleton, Inc.*, 311 F.3d at 1388.

Instead, in response to the Examiner, Abbott amended the claims to "to incorporate limitations of the dependent claims which the Examiner [] indicated do not interfere with the claims of the '994 application." (*See* Gunther Reply Decl., Ex. 9 at 16.) That is, Abbott amended the pending claims to distinguish them from the claims in ***Centocor's*** pending application, which did not claim a pharmaceutical composition, a pharmaceutically acceptable carrier or an additional agent. (*See id*; Gunther Reply Decl. Ex. 10 at 3.)[2] Specifically, Abbott amended claim 142 as follows:

> 142. (Currently Amended) ~~An~~ A pharmaceutical composition comprising an isolated human antibody, or antigen-binding portion thereof, which is capable of binding to an epitope of the p40 subunit of IL-12 and an additional agent.

(Gunther Reply Decl., Ex. 9 at 3 (underlined language added and crossed out language deleted).)

There is simply no factual support in the record for Centocor's allegation that the "additional agent" limitation was included by Abbott to distinguish over claims that recited "a pharmaceutically acceptable carrier." Absent such a clear and unmistakable statement, Abbott cannot be found to have surrendered "pharmaceutically acceptable carrier" from the scope of

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[2] Centocor's claims were to:

1. An isolated human antibody, or an antigen-binding portion thereof, that binds to human IL-12, wherein said human antibody is a neutralizing antibody.

102. An isolated human antibody, or antigent-binding portion thereof, which disassociates from human IL-12 with a K_D of 1 x 10^{-10}M or less, as determined by surface Plasmon resonance.

103. An isolated human antibody, or an antigen-binding portion thereof, which disassociates from human IL-12 with a K_D of 1 x 10^{-10}M or less and binds to an epitope of the p40 subunit of human IL-12.

(Gunther Reply Decl., Ex. 10 at 3.)

"additional agent." *See Voda*, 536 F.3d at 1321; *Golight, Inc.*, 355 F.3d at 1332; *Middleton, Inc.*, 311 F.2d at 1388.

Instead, Centocor's argument is based on speculation and inference. Centocor appears to be arguing that because claim 64 of Abbott's '128 patent (which recites an antibody and a pharmaceutically acceptable carrier) was deemed to interfere with the claims of Centocor's '994 application, and because the Patent Examiner was presumably satisfied that amended claim 1 of the '485 patent (which recites an antibody and an additional agent) did not interfere with the claims of Centocor's '994 application, then, by extension, "'pharmaceutically acceptable carrier' and 'additional agent' have to mean something different." (*See* Def. Br. at 18.) But statements by the Patent Examiner, and inferences made from the Examiner's silence, are not proper basis upon which to construe a claim term. *See Innova/PureWater, Inc.*, 381 F.3d at 1124; *DeMarini Sports*, 239 F.3d at 1326.

Nor is there any evidence in the prosecution history that would prohibit "pharmaceutically acceptable carrier" from being understood to be a subset of "additional agent." That is, while an "additional agent" may be "pharmaceutically acceptable carrier"– for example, "an agent which effects the viscosity of the composition" – "additional agent[s]" could also be something that is not a "pharmaceutically acceptable carrier." One such example set forth in the specification are non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. (col. 75, ll.59-65, col. 76, ll.3-12.) Put another way, while a "pharmaceutically acceptable carrier" may always also be an "additional agent", an "additional agent" may or may not be a "pharmaceutically acceptable carrier."

Thus, at a minimum, the prosecution history relied upon by Centocor is "subject to multiple reasonable interpretations" as to the relationship between "pharmaceutically acceptable

carrier" and "additional agent." *See Golight, Inc.*, 355 F.3d at 1332. Federal Circuit law is clear that in such circumstances there is no "clear and unmistakable" disavowal, and thus no prosecution disclaimer. *See id.*; *Cordis Corp.*, 339 F.3d at 1359.

III. CONCLUSION

For the reasons set forth in Abbott's opening brief and herein, Abbott respectfully requests the Court construe the terms as follows:

CLAIM TERM:	ABBOTT'S PROPOSED CONSTRUCTION:
"neutralizing antibody"	"an antibody whose binding to an antigen results in inhibition of a biological activity"
"inhibits phytohemagglutinin blast proliferation in an in vitro PHA assay" or "inhibits phytohemagglutinin blast proliferation in an in vitro phytohemagglutinin blast proliferation assay (PHA) assay"	"inhibits the proliferation of stimulated human PHA blasts"
"inhibits human IFNγ production"	"inhibits human IFNγ production in either an *in vitro* or *in vivo* assay"
"inhibits IL-12 binding to its receptor in an IL-12 receptor binding assay (RBA)"	Plain meaning
"additional agent"	Plain meaning

CLAIM TERM	AGREED UPON CONSTRUCTION
"Kd"	"the dissociation constant of a particular antibody-antigen interaction"
"koff"	"the off rate constant for dissociation of an antibody from the antibody/antigen complex"
"surface plasmon resonance"	"an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix"
"recombinant antibody"	"antibody that is prepared, expressed, created or isolated by recombinant means"
"pharmaceutically acceptable carrier"	"any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible, including one or more of water, saline, sugars, alcohols, polyalcohols, wetting or emulsifying agents, preservatives or buffers."

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CERTIFICATE OF SERVICE

I certify that, on October 4, 2010, this document (filed through the ECF system) will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF).

/s/ Robert J. Gunther, Jr.